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REVIEW ARTICLE

Alzheimer: A Decade of Drug Design. Why Molecular Topology can be an Extra Edge

Riccardo Zanni[a,b], Ramon Garcia-Domenech[a], Maria Galvez-Llompart[a,b] and Jorge Galvez[a,*]

[a]*Molecular Topology and Drug Design Unit. Department of Physical Chemistry, University of Valencia, Valencia, Spain;* [b]*Department of Microbiology, University of Malaga, Malaga, Spain*

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***Abstract: Background*:** The last decade was characterized by a growing awareness about the severity of dementia in the field of age-related and no age-related diseases and about the importance to invest resources in the research of new, effective treatments. Among the dementias, Alzheimer's plays a substantial role because of its extremely high incidence and fatality. Several pharmacological strategies have been tried but still now, Alzheimer keeps being an untreatable disease. In literature, the number of QSAR related drug design attempts about new treatments for Alzheimer is huge, but only few results can be considered noteworthy. Providing a detailed analysis of the actual situation and reporting the most notable results in the field of drug design and discovery, the current review focuses on the potential of molecular topology as a reliable tool in finding new anti-Alzheimer *lead* compounds.

***Methods*:** Published works on QSAR applied to the search of anti-Alzheimer's drugs during the last 10 years has been tracked. 2D and 3D-QSAR, HQSAR, topological indexes, etc. have been analyzed, as well as different mechanisms of action, such as MAO, AchE, *etc*. An example of topological indexes' application to the search of potential anti-Alzheimer drugs is reported.

***Results*:** Results show that QSAR methods during the last decade represented an excellent approach to the search of new effective drugs against Alzheimer's. In particular, QSAR based on molecular topology allows the establishment of a direct structure-property link that results in the identification of new *hits* and *leads*.

***Conclusion*:** Molecular topology is a powerful tool for the discovery of new anti-Alzheimer drugs covering simultaneously different mechanisms of action, what may help to find a definitive cure for the disease.

Keywords: Alzheimer, molecular, topology, drug, design, QSAR.

1. INTRODUCTION

Dementia is not a specific disease but a denomination for deterioration in mental capability severe enough to interfere with daily life. It describes a broad range of symptoms related with a decline in memory or other thinking skills leading to reduce a person's ability to perform everyday activities. Alzheimer's disease (AD) accounts for 60 to 80 % of cases of dementia. Vascular dementia, which happens following a stroke, is the second most prevalent dementia type, but there are several other conditions that can lead to symptoms of dementia, including reversible ones, such as thyroid problems and vitamin deficiencies [1].

Dementia is often mistakenly referred to as "senility" or "senile dementia," which reveals the formerly universal but wrong belief that severe mental decay is a typical aspect of aging. Alzheimer's is not just a disease related to old age. Younger-onset, also known as early-onset, Alzheimer's affects people under 65, and it is estimated that up to 5% of the more than 5 million Americans with Alzheimer's, have younger-onset [1]. Many people with early onset are in their 40s and 50s and they have families, careers or are even have to take care of themselves when Alzheimer's disease strikes.

It is currently estimated that 46.8 million people worldwide have dementia with a global cost at US$818 billion in 2010. By 2030, it is estimated that there will be 74.7 million people with dementia, and the burden of caring for these individuals could rise to some US$2 trillion [2].

*Address correspondence to this author at the Department of Physical Chemistry, Faculty of Pharmacy, University of Valencia, P.O. 46100, Burjassot, Spain; Tel/Fax: +34-963544891; +34-963544892;
E-mail: Jorge.galvez@uv.es.

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Despite the large number of *hit* and *lead* compounds identified *in silico* and the development of many clinical trials [3], only four cholinesterase inhibitors and memantine have demonstrated sufficient safety and efficacy to allow marketing approval at international level. These five agents are symptomatic treatments, temporarily ameliorating memory and thinking problems being their clinical effect limited; they do not treat the underlying cause of AD and do not slow the rate of incidence [4].

AD drug failures are due to lack of sufficient target engagement or to toxic effects. Efforts to bring new AD drugs to market have failed because a number of causes such as incomplete understanding of AD pathogenesis, the multifactorial aetiology and complex pathophysiology of the disease, the slowly progressive nature of AD and the high rate of comorbidity within the elderly population [2].

1.1. QSAR (Quantitative Structure Activity Relationships)

QSAR stands for the establishing quantitative relationships between molecular structure and activity, using mathematical equations. The present review analyzes the contribution of QSAR to the discovery of novel anti-Alzheimer drugs during the last 10 years. Moreover, given the notable performance demonstrated by QSAR based on Molecular Topology (MT), a significant part of this review will be devoted to MT-QSAR as a strategic tool to discovery new effective drugs against Alzheimer.

There is general consensus that QSAR born in 1964, when Corwin Hansch and Toshio Fujita [5] introduced the idea that the experimental properties of molecules could be expressed as a function of different physicochemical parameters capable to evaluate electronic and steric characteristics. This way they coined the concept of quantitative structure-activity relationships (QSAR).

So, QSAR analysis is a study correlating the properties or activities of compounds with their structures employing the interdisciplinary knowledge of chemistry, mathematics, biology and physics. The idea is to establish one or several equations which correlate the real property or activity, expressed either as a categorical or a quantitative way, with a set of molecular descriptors whose nature can be physical, physicochemical or even purely mathematical (topological). Within this framework, any physical, chemical or biological property of compounds can be mathematically related to their structure and thereby to the structures of new or novel compounds (they may even have not a physical existence).

This way, using the properties of known molecules we can find new or novel compounds showing better properties [6] and that can be done by screening molecular databases or designing *ex novo* novel compounds.

Many QSAR models employ 2D-descriptors; among them stand as the most relevant the topological descriptors, also called graph invariants. The invariance of a molecular descriptor means that its value is independent of the particular characteristics of the molecular representation, such as atom numbering or labelling, spatial reference frame, molecular conformations, etc. Invariance is assumed in QSAR as a basic requirement for any descriptor [7]. This is particularly important for topological indices, which are descriptors derived from molecular topology. MT can be defined as a part of mathematical chemistry consisting of the topological description of molecular structures under the graph-theory framework. Such description deals mainly with the connectivity of the atoms in the molecule and must be based on numerical descriptors, which are invariant under deformation or in general under any three-dimensional (3D) feature. Physical or physicochemical magnitudes as molecular descriptors are not considered in this scenario [8].

In Fig. (**1**), a simple molecule such as isopentane is represented as a graph. In a graph, atoms are represented by points called vertices and bonds by segment named edges. Once a graph is created, it is transformed into a matrix called topological or adjacency matrix, which is calculated by labelling with an ordinal number each of graph vertices. Then, the matrix is built so that any entry *ij* has value 1 if there is an edge or link between vertices *i* and *j;* otherwise it is 0.

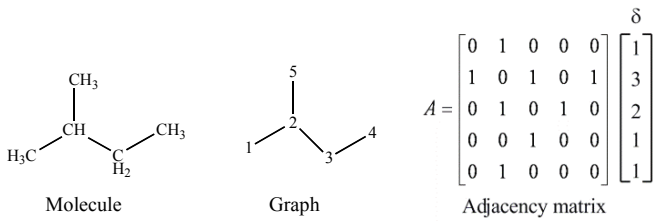


Fig. (1). The graph for isopentane and its relative adjacency matrix.

MT's advantages can be summarized as follows [9]:

- Molecular structure is depicted in single mathematical (matrix) terms.
- The procedure is easily computerized.
- The approach enables the quick and accurate screening of large number of compounds as well as the design of novel ones by the reverse process (property → structure).

This way, graph theory and surrounding disciplines stand as basic tools for MT development.

Finally, the 3D-QSAR has emerged as a natural extension to the classical Hansch and Free-Wilson approaches, which exploits the three-dimensional properties of the ligands to predict their biological activities using robust statistical techniques such as PLS (Partial Least Squares), generalized PLS, ANN (Artificial Neural network), *etc* [10].

Fig. (**2**) shows a standard layout for a typical QSAR study. The first step consists of the data collection. After that, molecular descriptors are calculated and one or more predictive models are developed. The robustness of the models is checked and if the desired level of quality is met, models are applied first on a test set and then on the virtual screening in databases searching for new molecules. The goal is usually the identification of new *hit* and *lead* compounds.

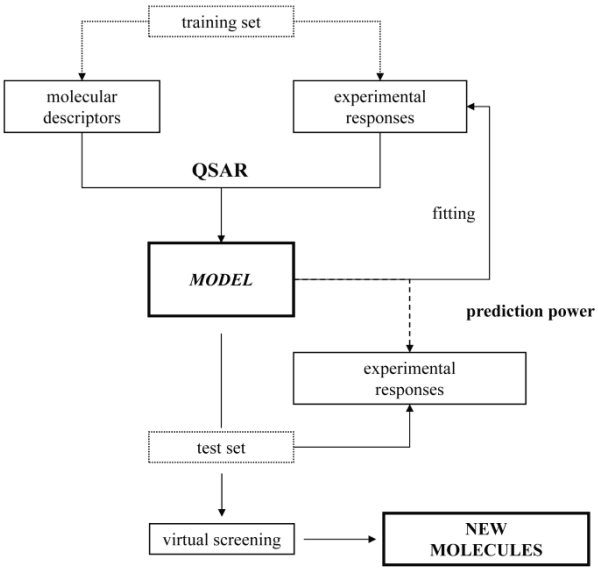


Fig. (2). A schematic example of QSAR strategy.

2. ALZHEIMER - 10 YEARS OF QSAR

2.1. 2D QSAR Studies

A compelling register of last 10 years essential results in the field of 2D QSAR is reported. Topological and other 2D descriptors will be considered. In order to make easier the reader comprehension, results will be addressed in chronological order.

2.1.1. 2007-2011

In 2008 Saracoglu and Kandemirli investigated the structure-activity relationships for a class of acetyl cholinesterase (AchE) inhibitors related to tacrine, using the Electron-Topological Method (ETM) (see Fig. **3**) [11]. Optimized geometry data and electronic characteristics for a series of tacrine analogues were used for ETMs study. A set of 44 molecules were collected. According to the activity level, molecules under study were divided into 3 groups:

1. Active compounds (20 molecules with $IC_{50} \leq 1.3\mu M$);
2. Low active compounds (4 molecules with $1.3 > IC_{50} < 3.7\mu M$);
3. Inactive compounds (20 molecules with $IC_{50} \geq 3.7\mu M$) compounds.

The structural parameters responsible for the activity form a matrix called electron topological sub matrix of activity (ETSA), and are derived from an ETMC that represents one of the most active compounds ("a template" for comparison). For each template compound, its ETMC was compared with the ETMCs of the rest of compounds in the three series mentioned above. Based on pharmacophores and anti-pharmacophores calculated as sub-matrices encoding important information from the spatial and quantum-chemical viewpoints, a system for activity prediction is developed. The system was tested on a few compounds with molecular skeletons other than those that were characteristic of the training sets. This allows identifying the presence/absence of human AChE binding affinity, at a level of probability of 84-89%, for structurally heterogeneous molecules. The initial data analysis reveals a close relation between activity and spatial and electronic characteristics of molecules. Any changes in the values of the matrices exceeding the limits allowed, because diminishing or complete loss of activity.

In 2009, a work by Solomon *et al.* presented a QSAR study on a series of 88 N-aryl derivatives which display inhibitory activity towards both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) [12]. Fig. (**4**) shows some N-aryl derivatives used in this QSAR study.

QSAR models were derived for 53 and 61 compounds for each target, respectively, with the aid of genetic function approximation (GFA), which is an approach that uses topological, molecular shape, electronic and structural descriptors. The predictive ability of the QSAR model was evaluated using a test set of 26 compounds for AChE (r^2=0.860, r^2_{pred} = 0.857 and q^2 = 0.803) and 20 compounds for BChE (r^2=0.880, r^2_{pred} = 0.882 and q^2 = 0.857). The QSAR models point out that AlogP98, Wiener, Kappa-1-AM, Dipole-Mag, and $^1\chi$ are important descriptors effectively describing the bioactivity of the compounds (see Eq. 1 and Eq. 2).

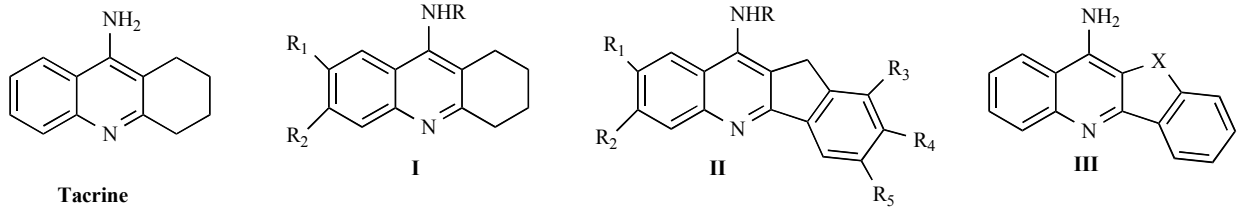


Fig. (3). Set of Tacrine Analogues used in the ETMC study.

$$pK_{iAchE} = 3.05 + 0.005(WIENER) + 0.23(ALOGP98) - 4.18(\,^3\chi_c^v) - 0.55(PHI) \quad \text{Eq. 1}$$

$$pK_{iBchE} = 3.79 - 0.60(KAPPA - 1 - AM) + 0.005(WIENER) + 0.33(\,^1\chi) + 0.04(DIPOLE - MAG) + 0.25(ALOGP98) \quad \text{Eq. 2}$$

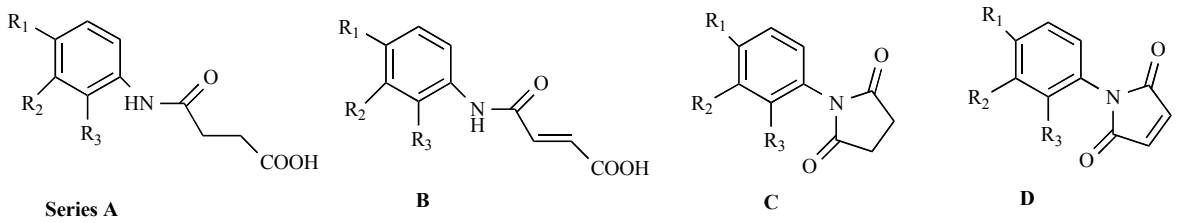


Fig. (4). QSAR study of N-aryl derivatives with varied inhibitory activity towards both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE).

Where:

WIENER = Graph–theoretical descriptor for the sum of chemical bonds between atoms; ALOGP98 = Thermodynamic descriptor for the logarithm of partition coefficient; $^{3}\chi_{c}^{v}$ and $^{1}\chi$= Molecular connectivity indices; PHI = Molecular flexibility indices; KAPPA-1-AM = Molecular shape kappa indices.

During the following year, Isela García, Yagamare Fall and Generosa Gómez used topological indices to predict new anti-Alzheimer and anti-parasitic GSK-3 inhibitors by multi-target QSAR through an *in silico* screening [13]. Several topological descriptors for a large series of 3370 active/non-active compounds were calculated with the ModesLab software. Linear Discriminant Analysis (LDA) was used to fit the classification function and predict activity in heterogeneous series of compounds. Among the most significant descriptors used in this work stand valence connectivity indexes ($\chi_1 V\ (P)$), Zagreb M indexes (M_1) and Balaban descriptor (J). LDA study for the selected topological function led to an overall accuracy of 91.1% in training series and 86.8% in validation series.

Also in 2010, Kumar and Bansal developed several QSAR studies on the estimation of monoamine oxidase-A inhibitory activity using topological descriptors [14].

Quantitative structure activity relationship analysis was performed with 32 synthetically derived analogues for their inhibitory effects on monoamine oxidase-A(see Fig. **5**), using two-dimensional topological descriptors.

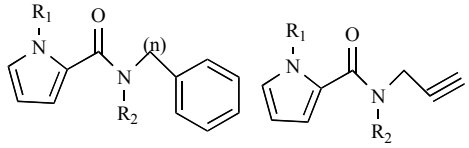


Fig. (5). Chemical structure of pyrrol – 2 carboxamide analogues used in the Kumar and Bansal work.

QSAR models were generated using multiple linear regression algorithms. Selected QSAR equation was:

$$K_i = 46.02 + 10.64(DECC) + 2.06(PHI) + 0.49(SPI) - 0.013(WAP) - 148.68(\chi_t) \quad \text{Eq. 3}$$

= 32 ; r^2 = 0.84 ; r^2_{adj} = 0.80 ; F = 26.23 ; $r^2_{(CV)}$ = 0.80 ; r^2_{pred} = 0.83 ; SEE = 0.95 ; q^2 = 0.88

Where:

DECC= Eccentric index; PHI= Kier Flexibility index; SPI=Superpendentic index; WAP= All-path Wiener index;Xt= Total structure connectivity index; n= number of compounds and F= Fisher distribution parameter.

As it can be seen, the correlation parameters reveal a good predictive capability of Equation (3). The cross-validation correlation parameter along with the q^2 correlation parameter satisfied a minimum of acceptance. Altogether, this research revealed significant correlation between MAO-A inhibitory activity and topological descriptors.

2.1.2. 2012-2017

The contributions about the importance of 2D descriptors in drug design during these years are many. The growing awareness on the effectiveness of topological indexes led many scientists to follow this approach as a reliable tool for the identification of novel *hit* and *lead* compounds.

In 2012 Bharate*et al.* [15] carried out a QSAR study for a series of meridianin analogues inhibiting Dyrk1A, just to find out structural features which are crucial for biological activity (see Fig. **6**). Dual-specificity tyrosine phosphorylation-regulated kinase 1A (Dyrk1A), is a protein kinase with diverse functions in neuronal development and adult brain physiology. High levels of Dyrk1A have been associated to the pathology of neurodegenerative diseases and are thought to be implicated in some neurobiological alterations of Down syndrome, such as mental retardation.

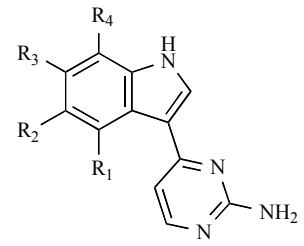
The selected regression function was:

$$pIC_{50} = 8.86 - 0.51(X1) - 0.01(X2) - 0.07(X3) - 0.27(X4) + 0.39(X5) \quad \text{Eq. 4}$$

Where:

X1=Kier Chi4 path/cluster index; X2=Total lipole; X3= VAMP polarization ZZ component; X4=Dipole moment Z component and X5=logP.

QSAR model shows a good correlation coefficient (r > 0.9), high F value (F > 20) and an excellent predictive power (r^2_{cv} and r^2_{pred}> 0.6). Activity of naturally occurring meridianins was also predicted. The study shows that Kier's Chi4



Meridianin A: R_1 = OH, R_2 = R_3 = R_4 = H
Meridianin B: R_1 = OH, R_2 = R_4 = H,R_3 = Br
Meridianin C: R_1 = R_3 = R_4 = H, R_2 = Br
Meridianin D: R_1 = R_2 = R_4 = H, R_3 = Br
Meridianin E: R_1 = OH, R_2 = R_3 = H, R_4 = Br
Meridianin F: R_1 = R_4 = H, R_2 = R_3 = Br
Meridianin G: R_1 = R_2 = R_3 = R_4 = H

Fig. (6). Structures of meridianin A-G.

path/cluster, total lipole, VAMP polarization ZZ component, dipole moment Z component and log P, play important role in Dyrk1A inhibition.

The same year Chitranshi *et al.* [16] developed a study to discover new inhibitors of the acetylcholinesterase (AChE). The quantitative structure–activity relationship (QSAR) equation was developed based on 44 AChE inhibitors: 34 training set compounds and 10 test set compounds (see Fig. **7**).

The model was developed using five information-rich descriptors—HBA, log P, HOF, EE, and dipole—which are important in determining AChE inhibitory activity. QSAR model (Eq. 5) yielded good statistical data, $r^2 = 0.723$; $q^2 = 0.703$; N = 34 for training set.

$$pIC_{50} = 5.47 + 9.48(HBA) + 9.95(logP) + 1.54(HOF) + 1.25(EE) - 1.72(DIPOLE) \quad \text{Eq. 5}$$

Where:

HBA = Hydrogen bond acceptor; log P = Solubility; HOF = Heat of formation in kcal; DIPOLE = Dipole moment in Debye; EE = Electronic energy in electron volt.

This model was further validated using leave-one-out cross-validation approach, Fischer statistics, Y randomisation test and prediction based on the test data set. A comprehensive docking study was also carried out, using different AutoDock softs.

Probably, one of the most relevant results obtained in the field of 2D drug design is the one by Galvez *et al.* in 2014 in collaboration with Pasinetti and the Mount Sinai School of Medicine of New York [17]. In that paper, the use of molecular topology led to the identification of several brand new anti-Alzheimer compounds with dual activity, namely β-amyloid (Aβ)-lowering and anti-oligomerization activities. Eight of the molecules were subsequently patented (see Fig. **8**), what represents a record in finding novel anti-Alzheimer molecules.

This is also a good example of using MT-QSAR to combine pre-existing data with molecular structure, to develop a mathematical characterization of the desired functional outcome, based on a specifically defined set of biological properties and/or therapeutic targets.

In 2015, Toporova *et al.* employed the QSAR models for the pIC_{50} (binding affinity) of 233 gamma-secretase inhibitors (see Fig. **9**), jointly with the Monte Carlo method using CORAL software. Their results showed the synergy derived from the joint use of the two methodologies to select novel potential gamma-secretase inhibitor [18].

2.2. 3D QSAR Studies

The other main branch of QSAR, is about 3D descriptors. It takes into account 3D properties such as polarizability and chirality. Moreover, it deals with structure based techniques such as docking, molecular dynamics and pharmacophore design.

2.2.1. 2007-2011

In 2008, Kim *et al*. developed a three-dimensional common feature pharmacophore model by using HipHop program provided in Catalyst software. Subsequently, it was used as a query for screening database in search of novel GSK-3b inhibitors [19]. Sequential virtual screening procedure (SQSP) was conducted by applying the common feature pharmacophore and RP model. The final 56 hit compounds were carefully selected considering the expected docking mode in crystal structures. Subsequent enzyme assay for human GSK-3b protein confirmed that three of the compounds exhibited inhibitory activity at the micromolar level (see Fig. **10**).

The work by Mathura *et al.* in 2010, led to a 3D-QSAR model used to identify, in a dihydropyridine-like compound library, novel inhibitors of amyloid beta (Aβ) production

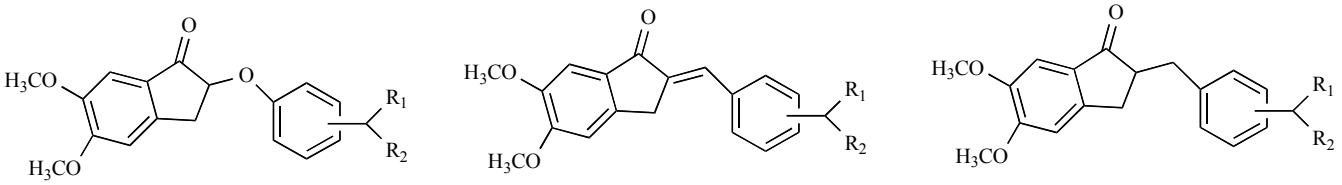


Fig. (7). Structure of 1-indanone derivatives as AChE inhibitors.

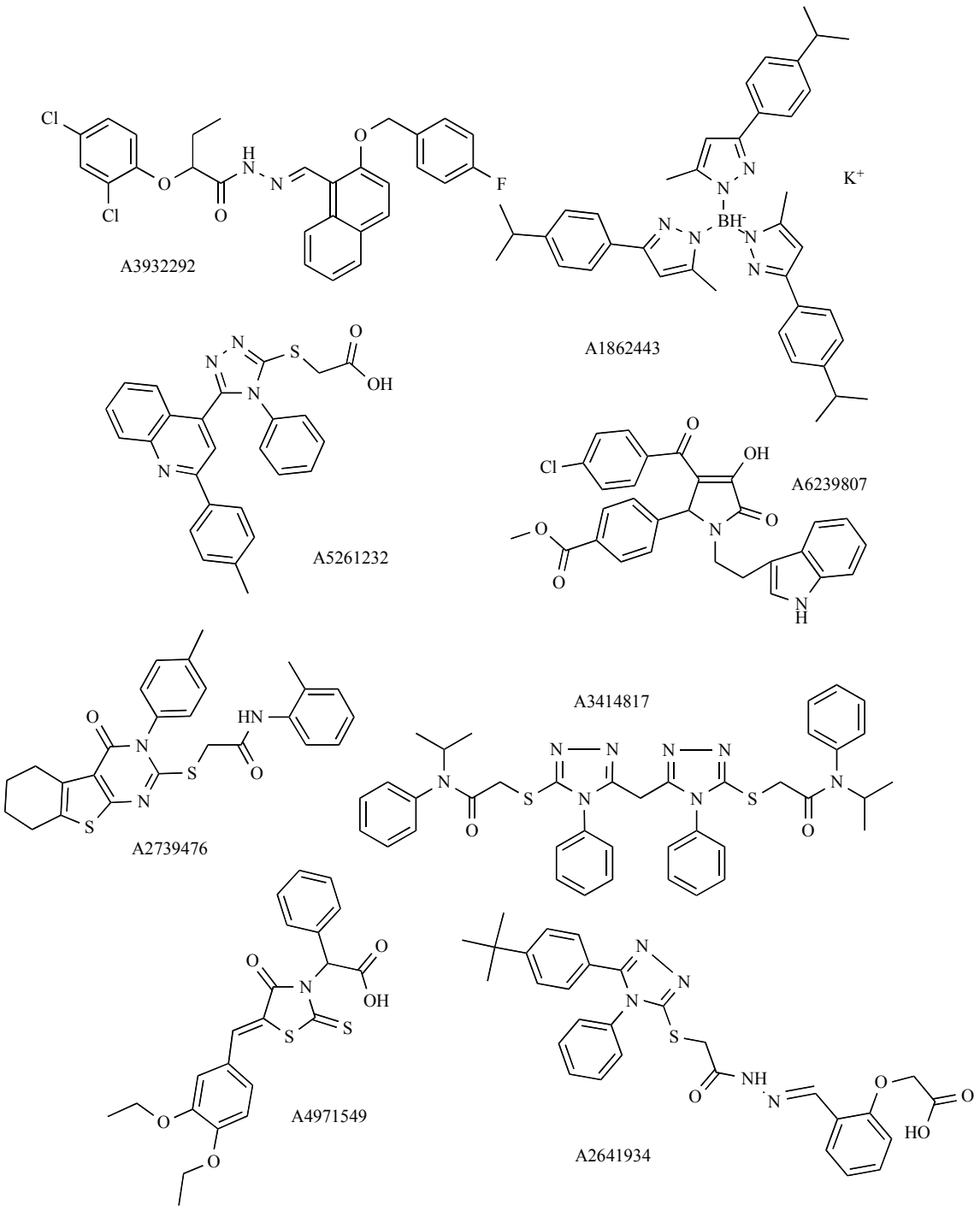
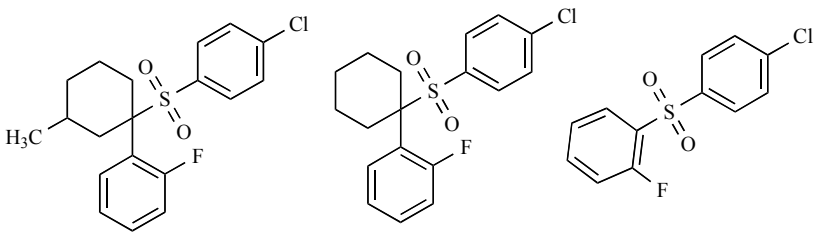


Fig. (8). Structures of eight compounds that are able to exert dual Aβ-lowering and anti-oligomerization by *in vitro testing* [17].

[20]. A set of 24 compounds analogues to 1,4dihydropyridine (DHP) showing Aβ inhibitory activity, were used as training set. From them, a 3D-QSAR model was built up using the Phase soft. (SchrÖdinger, USA). The model performed very well in a test set of compounds.

Fig. (**11**) shows five pharmacophore points for dihydropyriden analogues.

Moreover, they used the model to screen a 1043 DHP-like compounds library, finding that the model can effectively find out potent *hits*. The *in vitro* screen distribution of compounds at 5 μM, showed 56 SH compounds that inhibited Aß by more than 90%, 146 compounds showed a medium potency, 173 a low potency and 668 were classified as inactive. The *in silico* screen was carried out on the 100 top and bottom compounds based on their predicted potency. Among the 100 bottom compounds, 99% showed no Aβ lowering activity and only one displayed marginal Aβ lowering activity (20% inhibition at 5 μM). Within the top 100 compounds, the model identified over 66% of active compounds, among



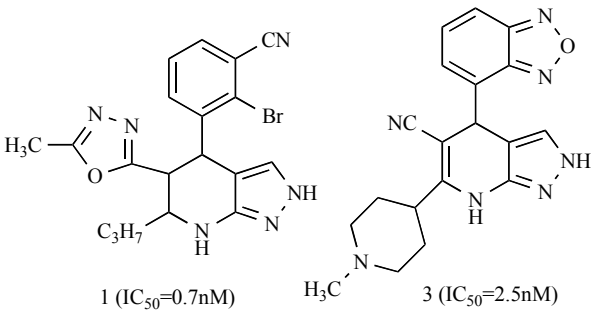
CSID:23259043, CHEMBL191246

Fig. (9). Examples of effective modifications of the molecular structure derived from Toporova *et al*. work (ID CHEMBL191246, pIC_{50}=7.26).

them 18 were the most potent in the library. The probability of finding SH compounds in the top 100 is three times greater using the QSAR model as compared to a "by chance" finding. Finally, authors set out to screen a small focused library of DHP like molecules and determined their IC_{50} for Aβ production. The best 3D-QSAR model was able to predict the test set with a correlation coefficient of 0.7.

2.2.2. 2012-2017

In 2012, three works are reported in which 3D-QSAR studies were carried out to predict anti-Alzheimer properties. In one of them, Hajjo *et al.* [21] presented a chemocentricinformatics approach to drug discovery focused on the identification and experimental validation of selective estrogenic receptors modulators as ligands of 5-hydroxytryptamine-6 receptors and as potential cognition enhancers. Several databases were used, as for instance DrugBank and PubChem, to build up the dataset. Then, several combinatorial techniques were used to generate the regression equations. The first approach relied on k-nearest neighbour (kNN) model optimization method using Dragon's descriptors, and the second was a classification based on association (CBA) and subgraphs (SG) descriptors. Once the equations were obtained, a virtual screening on both the 59000 molecules within the WDI chemical library and 1300 DrugBank compounds included in the cmapdatabase was carried out. Subsequently, Connectivity Map for potential anti-Alzheimer agents was used.



1 (IC_{50}=0.7nM) 3 (IC_{50}=2.5nM)

Fig. (10). Some structures and activities of GSK-3b inhibitors used for pharmacophore generation.

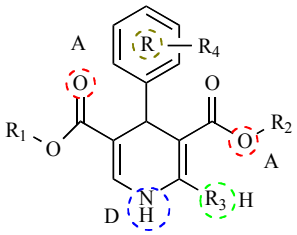


Fig. (11). The five point pharmacophore points identified: Hydrogen acceptor sites (A), hydrogen donor site (D), hydrophobic site (H) and aromatic group feature (R).

Fig. (**12**) shows some of the compounds selected, which are related to several therapeutically classes.

The paper by Souza *et al.* introduced the use of hologram QSAR models to identify novel potential anti-Alzheimer agents [22]. A series of 36 inhibitors (29 training set and 7 test set compounds) of acetyl/butyrylcholinesterase (AChE/BChE),were used to build the models. A data set of 36 4-[(diethylamino) methyl]-phenol AChE/BChE inhibitors was compiled from the work of Yu *et al.* [23]. The HQSAR models (N = 29) exhibited significant cross-validated (AChE, q^2 = 0.787; BChE, q^2 = 0. 904) and non-cross-validated (AChE, r^2 = 0.965; BChE, r^2 = 0.952) correlation coefficients.

The best HQSAR model for the AChE inhibitors was generated using bonds (B) and connections (C) as fragment distinction parameters and 9–12 as the fragment size, showing q^2 = 0.787 and r^2 = 0.965. For the BChE inhibitors, the best HQSAR model was developed using atoms (A) and bonds (B) as fragment distinction parameters and 9–12 as the fragment size, showing q^2 = 0.904 and r^2 = 0.952.

A complete HQSAR analysis involves the investigation of important molecular fragments directly related to the biological activity variation so that one may suggest structural modifications. Thus, the HQSAR models can be graphically displayed as color-coded structure diagrams in which the colour of each atom reflects its contribution to the potency variation. The red and green ends of the spectrum correspond to negative and positive contributions respectively, whereas atoms with intermediate contributions are white [15]. The most active compounds, in terms of individual atomic contributions as (compounds 26 and 24), selected according to the best HQSAR models, are displayed in Fig. (**13**).

Contribution maps show that structural fragments containing aromatic moieties and long side chains increase potency.

Finally, the same year, Liu *et al.* explored the binding of BACE-1 inhibitors using comparative binding energy analysis

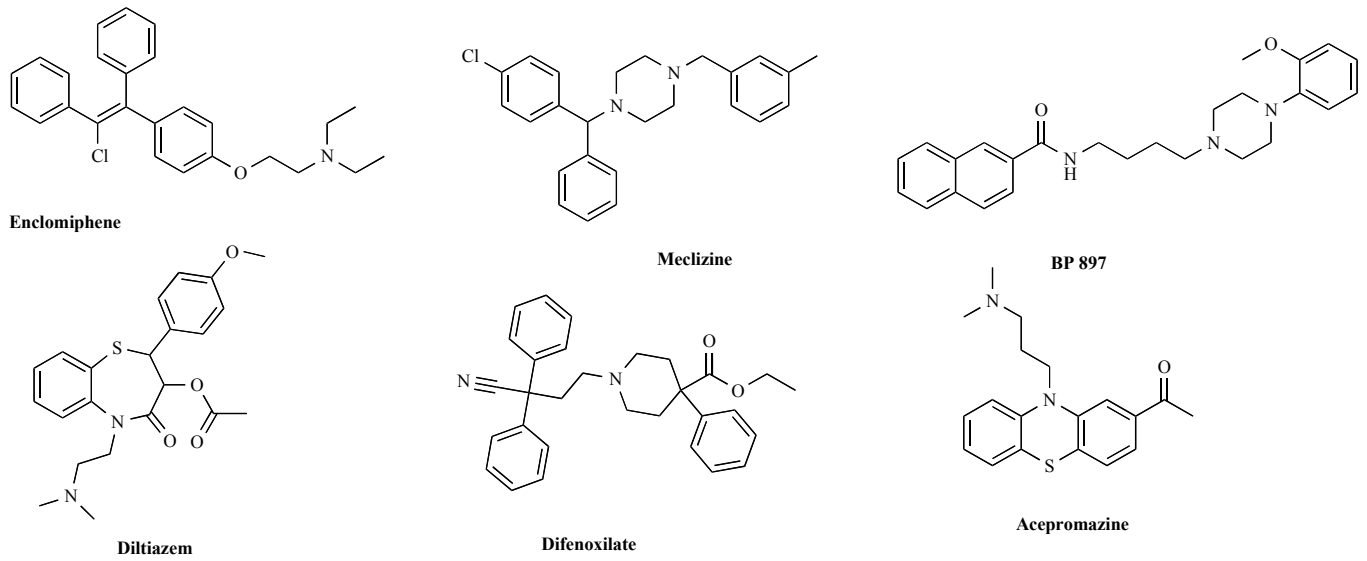


Fig. (12). Some compounds of different therapeutic classes obtained from QSAR-based VS and cmap.

(COMBINE) [24]. The inhibition of β-secretase (BACE-1) activity is a potentially important pathway for Alzheimer's treatment. To explore the mechanism of inhibition, the authors describe the use of 46 X-ray crystallographic BACE-1/inhibitor complexes to derive quantitative structure-activity relationship (QSAR) models. The inhibitors were aligned by superimposing 46 X-ray crystallographic BACE-1/inhibitor complexes, and gCOMBINE software was used to perform COMparativeBINding Energy (COMBINE) analysis on these 46 minimized BACE-1/inhibitor complexes.

By considering the protein residues contributions to the electrostatic and van der Waals intermolecular interaction energies, two predictive and robust COMBINE models were developed: (i) the 3-PC distance-dependent dielectric constant model (built from a single X-ray crystal structure) with a q^2 value of 0.74 and an SDEC value of 0.521; and (ii) the 5-PC sigmoidal electrostatic model (built from the actual complexes present in the Brookhaven Protein Data Bank) with a q^2 value of 0.79 and an SDEC value of 0.41.

Fig. (**14**) shows the chemical structure and biological activity of the three most active compounds of the data set of 46 co-crystallized ligands of BACE-1.

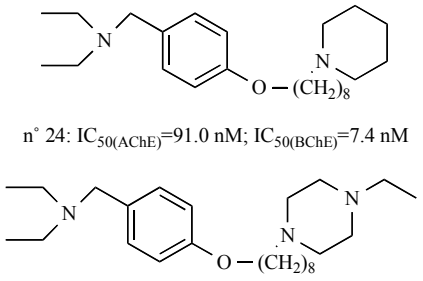


Fig. (13). Chemical structures and biological activity (IC_{50}, nM) for the 4-[(diethylamino) methyl]-phenol analogues that were the most active as AChE and BChE inhibitors.

In 2013, Islam *et al.* compare quercetin with conventional AchE inhibitors to search for a better drug candidate through an *in silico* QSAR study [25] (see Fig. **15**). Physicochemical properties of conventional drugs and quercetin were predicted using bioinformatics tools. Molecular docking of these compounds on the active site of AchE was performed using AutoDock and comparative analysis was performed. Later, modification on the basic structure of quercetin with different functional groups was done to perform QSAR analysis. Quercetin showed a similar drug likeness score to the conventional drugs. The binding strength for quercetin in the active site of the enzyme was - 8.8 kcal/mol, which was considerably higher than binding scores for some of the drugs such as donepezil (binding score -7.9 kcal/mol). Fifteen hydrogen bonds were predicted between quercetin and the enzyme, whereas conventional drugs had fewer or even no hydrogen bonds. It implies that quercetin can act as a better inhibitor than conventional drugs. To improve the results, similar structures of quercetin were searched through SIMCOMP database and modified structurally. A methylation in the 4-OH position of the molecule showed better binding affinity than parent quercetin. The QSAR study indicated that O-4 methylation was specifically responsible for better affinity.

In 2014, an interesting article by Bautista-Aguilera *et al.* shows the design, synthesis, biochemical evaluation, ADMET, molecular modelling, and QSAR analysis of novel donepezil-pyridyl hybrids [26]. The 3D-quantitative structure-activity relationship study was used to define 3D-pharmacophores for the inhibition of MAO A/B, acetylcholinesterase (AChE), and butyrylcholinesterase (BuChE) enzymes and to design DPHs as novel multi-target drug candidates with potential impact in the therapy of AD.

One of the most interesting works is the one by Goyal *et al.* in 2014 [27]. It is relevant because along with the one by Galvez *et al.* [17] presents a QSAR study for the identification of new drugs against Alzheimer using a dualistic strate-

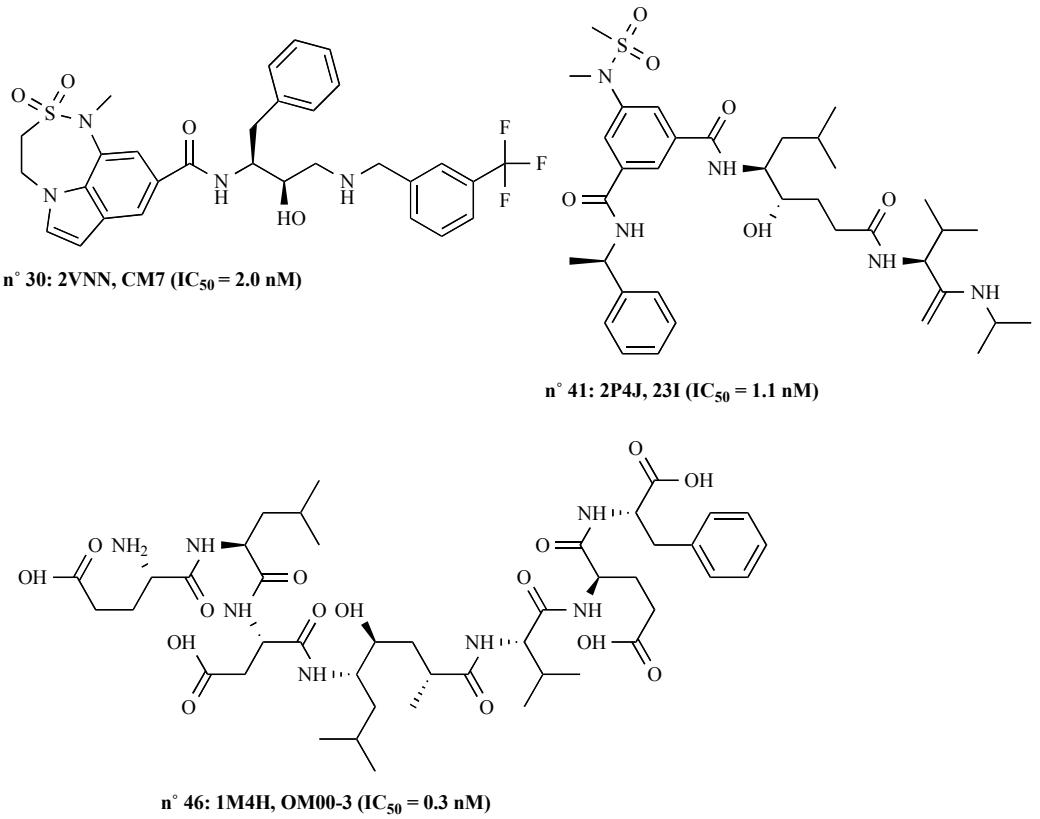


Fig. (14). Chemical structure and biological activity of three of the most active compounds of the data set of 46 co-crystallized ligands of BACE-1.

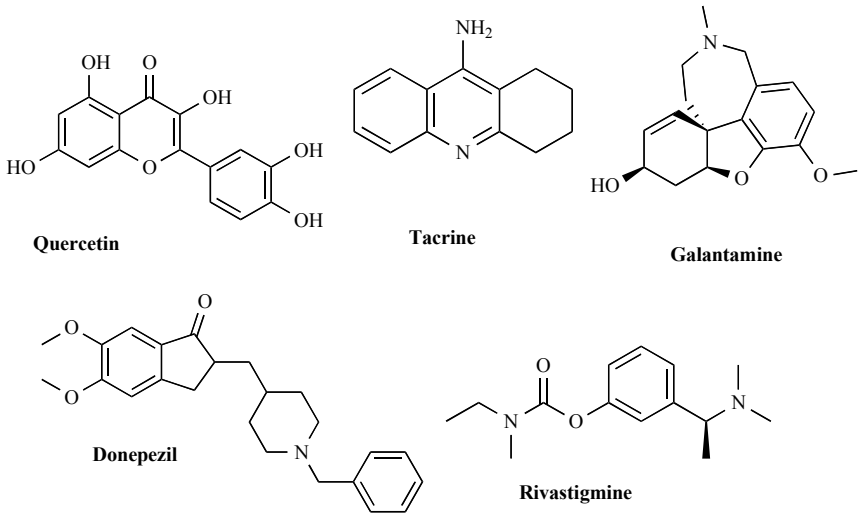


Fig. (15). Chemical structure of the 5 compounds under study.

gy. In contrast with the work by Galvez *et al*. this study uses 3D-QSAR descriptors. The main objective consisted of determine dual inhibitors of β-amyloid cleavage enzyme (BACE-1) and of acetylcholinesterase (AChE). To do so, fragment-based QSAR and molecular Docking were employed. The data set was made of a group of fragments of 20 1,4-dihydropyridine (DHP) derivatives. Descriptors were calculated and a large combinatorial library of DHP analogues was created. In this study, the convincing parametric values for GQSAR model were observed in terms of correlation coefficient $r^2 = 0.851$, predicted correlation coefficient $r^2_{pred} = 0.752$, cross-correlation coefficient $q^2 = 0.682$, and low standard error SE= 0.085, which implied that the model can be considered stable and accurate. Moreover, high values of other statistical parameters like F_{est}=34.4 provided additional support that the model was significant and robust with minimum chance of failure.

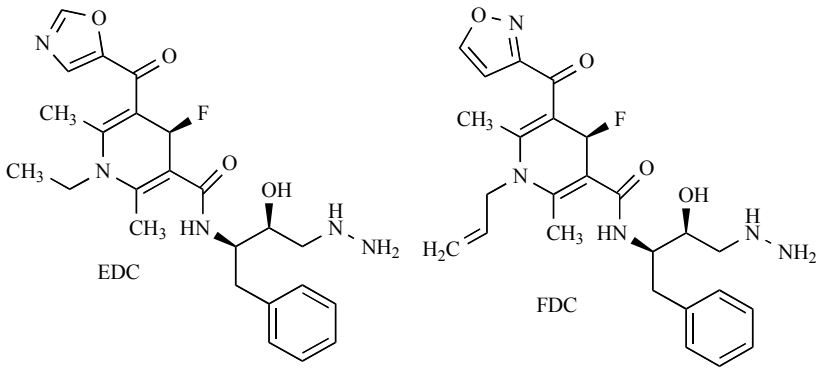


Fig. (16). Structure of selected molecules, EDC and FDC (1,4-dihydropyridine derivatives) possessing dual inhibitory property, BACE and AchE.

Docking studies for 3405 molecules of combinatorial library were carried out against AchE and BACE-1. Among these molecules, a total of 1310 and 1482 compounds having good binding affinity for BACE-1 and AChE, respectively, were identified using HTVS. After HTVS, the highest docking scores for both targets, BACE-1 and AChE, were found to be −10 kcal/mol and −12 kcal/mol, respectively. Compounds with Glide score above −8 kcal/mol for BACE-1 and −6 kcal/mol for AChE were then subjected to XP protocol for further refinement of Glide score. The two top scoring compounds, namely, (4R)-1-ethyl-4-fluoro-N- [(2R,3S)-4-hydrazinyl-3-hydroxy-1-phenylbutan-2-yl]-2,6- dimethyl-5-(1,3-oxazole-5-carbonyl)-1,4-dihydropyridine-3- carboxamide and (4R)-4-fluoro-N-[(2R,3S)-4-hydrazinyl-3- hydroxy-1-phenylbutan-2-yl]-2,6-dimethyl-5-(1,2-oxazole-3- carbonyl)-1-(prop-2-en-1-yl)-1,4-dihydropyridine-3-carboxamide(further referred to as EDC and FDC, resp) were found possessing dual target inhibitory capability (see Fig. **16**).

The very same year, Hung *et al.* made an *in silico* screening on compounds belonging to traditional Chinese medicine. The objective was to identify new molecules able to inhibit histone deacetylase 2 in patients with Alzheimer [28]. Three prediction models were used: multiple linear regression (MLR), support vector machine (SVM), and the Bayes network toolbox (BNT). Moreover, Molecular dynamics simulation provided the protein-ligand interactions of compounds. The bioactivity predictions of pIC50 values suggest that the TCM candidates m (−)-Bontlferulate, monomethylcurcumin, and ningposides C, have a greater effect on HDAC2 inhibition (see structures in the Fig. **17**). Authors found that there was a great influence of hydrogen bonds and hydrophobic moieties on the protein-ligand interactions.

In the same year as well, Valasani *et al.* used several 2D and 3D-QSAR approaches to study the identification of novel Cyclophilin D inhibitors [29]. To be exactly, they developed a structure-based design and synthesis study through pharmacophoremodelling, virtual screening and molecular docking. Since appropriately designed small organic molecules might bind to CypD and block its interaction with Aβ, 20 trial compounds were designed using known procedures that started with basic pyrimidine and sulfonamide scaffolds known to have useful therapeutic effects. 2D-QSAR was applied to 40 compounds with known IC_{50} values, which formed the training set, followed by a trial set of 20 designed compounds. A correlation analysis was carried out comparing the statistics of the measured IC_{50} with predicted values for both sets. Selectivity-determining descriptors were interpreted graphically in terms of Principal Component Analysis (PCA). These descriptors can be very useful for predicting activity enhancement for lead compounds. A 3D pharmacophore model was also created and molecular dynamics simulations were carried out for the 20 trial compounds with known IC_{50} values. Molecular descriptors were included in the 2D-QSAR studies using the Lipinski rule-of-five. Fifteen of the 20 molecules satisfied all 5 Lipinski rules, and the remaining 5 satisfied 4 of the 5 Lipinski criteria and nearly satisfied the fifth. Altogether, the use of 2D-QSAR, 3D pharmacophore models and molecular docking experiments

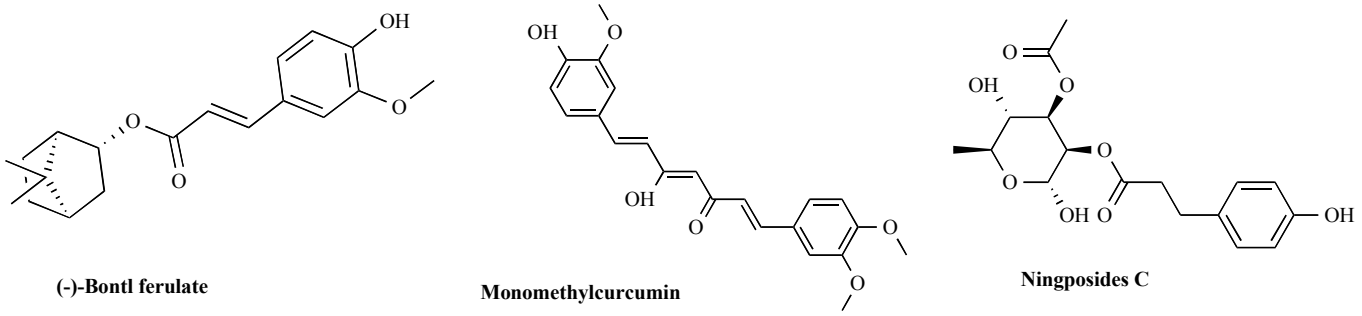


Fig. (17). Structures of TCM candidatesm with a greater effect on HDAC2 inhibition.

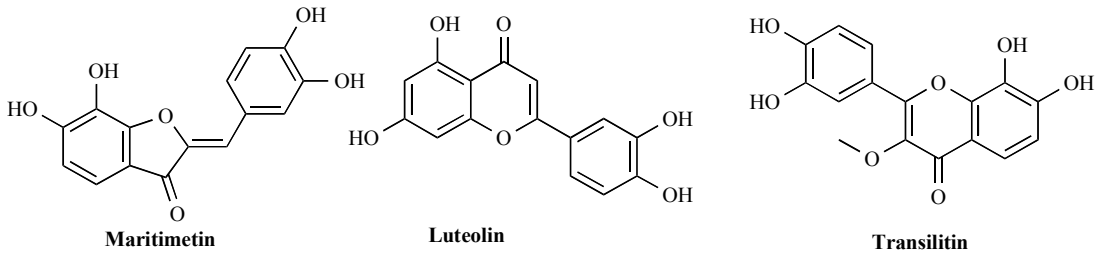


Fig. (18). Structures of the most active Aβ inhibitor molecules, Maritimetin, Luteolin, and Transilitin.

has demonstrated to be successful to predict activity, particularly for screening a large number of new compounds as active drug candidates.

Finally, in 2016 Mahmoodabadi and Ajloo developed a QSAR study using docking and molecular dynamics to study polyphenols as inhibitors of β-amyloid aggregation [30]. The inhibitory effect on amyloid-β aggregation was investigated on 25 polyphenolic compounds. After optimizing molecular geometry, it was employed Dragon 5.0 software to calculate the molecular descriptors. In order for variable selection, the multiple linear regression method (MLR) was performed based on the construction of a linear mathematical model with regard to the observed fibrillation constants. The dataset was randomly divided into two groups, training and test set.

The best regression Equation was:

$$\log(Fib) = -8.395(JGI2) - 0.522(Mor07v) + 0.122(RDF045v) - 0.087(DISPv) + 0.338(GATS6e) - 3.807 \quad \text{Eq. 6}$$

here:

JGI2 = Mean topological charge index of order2 (Galvez topol. charge indices); Mor07v = 3D-MoRSE—signal 07/weighted by atomic van der Waals volumes (3D-MoRSE descriptors); RDF045v = Radial distribution function - 4.5/weighted by atomic van der Waals volumes (RDF descriptors); DISPv = d COMMA2 value/weighted by atomic van der Waals volumes (Geometrical descriptors); GATS6e = Geary autocorrelation—lag 6/weighted by atomic Sanderson electronegativities (2D autocorrelations).

In this Equation, the presence of the so called autocorrelation indices, such as Mor7v and GATS6e is relevant.

Moreover, PCA analysis showed that considering five components (PC1−PC5) is a good choice because they explain over 88% of variance and the curvature of screen plot changes slowly and smoothly after PC5. Therefore, a model including five descriptors was chosen as illustrated following:

Where PC = Principal Components describing biological activities and molecular diversity of heterocyclic aromatic ring fragments.

To predict the binding energy of inhibitors to β-amyloid peptide, Autodock software was used. For each inhibitor, 250 independent docking runs were conducted. The setting of parameters was as follows: population sizes of 50, a maximum number of 25 million energy evaluations, a maximum number of 27000 generations, a cross-over rate of 0.8, elitism of 1 and a mutation rate of 0.02.

Docking studies on the polyphenolics derivatives showed that the binding pocket includes some amino acids such as Asp1, Glu3, Lys16, Leu17, Val18, Phe19, Phe20, Ala21, Glu22, Asp23, Ser26, and Asn27. Interaction modes between Aβ and the most active inhibitor molecules, namely Maritimetin 2, Luteolin 18, and Transilitin 22, were investigated (see Fig. **18**).

MD simulations were carried out by the GROMACS. Here, we describe simulation of Aβ (16–22) dimer in the presence of different inhibitors, focusing on the process of protein aggregation. The results revealed that compounds 2, 18, and 22, reduce protein aggregation and unfold enzyme structure. Therefore, interaction of these inhibitors with Aβ is stronger than that of compounds 3, 14, and 25.

2.3. Example of Application of Molecular Topology for the Search of Potential AD Agents

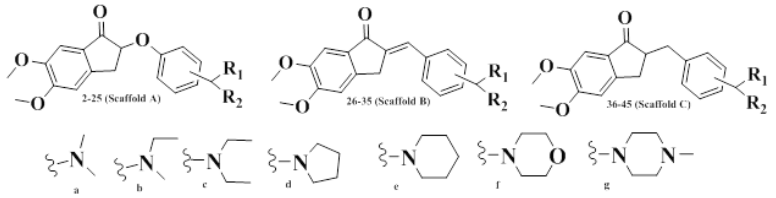
As a summary of what collected in this review, in this section, we present a practical example of application of MT-QSAR in the search of new active compounds for AD. Our target is acetylcholinesterase, AChE, and the enzymatic inhibition of a group of 44 1-indanone derivatives. The dataset together with donepezil (as reference drug), are listed in Table **1**, where can be realized that the AChE inhibitory activity (IC_{50}) ranges from 0.035 to 22.1 μM. All data were obtained from the reference [31].

Each molecule was drawn with the ChemDraw Professional 16.0.Software and stored in MDL Molfile format.Cpd: compound; P.:position; Scaff.: scaffold;-m:Meta;-p: Para.

In this study, the Kier and Hall topological connectivity indices have been used upto the fourth order, m(χ)t(indexes

$$log(Fib) = -0.040(PC1) + 0.028(PC2) - 0.043(PC3) - 0.147(PC4) - 0.030(PC5) + 1.687 \quad \text{Eq. 7}$$

Table 1. Structure and biological activities of 44 indanone derivatives as AChE inhibitors.



Cpd*	R_1	R_2	P.	Scaff.	IC_{50exp}(μM)	pIC_{50}exp	pIC_{50}calc
Donep.					0.02	7.80	
2	a	H	m-	A	1.10	5.96	5.81
3	a	CH3	m-	A	0.82	6.09	5.68
4	a	H	p-	A	0.21	6.68	6.57
5	a	CH3	p-	A	0.15	6.82	6.43
6	c	H	m-	A	2.28	5.64	6.14
7	c	CH3	m-	A	1.36	5.87	5.96
8	c	H	p-	A	0.10	7.00	6.90
9	c	CH3	p-	A	0.22	6.66	6.72
10	**d**	**H**	**m-**	**A**	**2.66**	**5.58**	**6.01**
11	d	CH3	m-	A	1.96	5.71	5.89
12	**d**	**H**	**p-**	**A**	**0.05**	**7.30**	**6.78**
13	d	CH3	p-	A	0.14	6.85	6.66
14	e	H	m-	A	3.18	5.50	5.80
15	e	CH3	m-	A	3.58	5.45	5.71
16	e	H	p-	A	0.15	6.82	6.57
17	**e**	**CH3**	**p-**	**A**	**0.13**	**6.89**	**6.48**
18	f	H	m-	A	14.6	4.84	5.05
19	f	CH3	m-	A	22.1	4.66	4.75
20	f	H	p-	A	1.30	5.89	5.84
21	f	CH3	p-	A	3.14	5.50	5.52
22	g	H	m-	A	6.41	5.19	4.95
23	**g**	**CH3**	**m-**	**A**	**17.6**	**4.75**	**4.76**
24	g	H	p-	A	1.42	5.85	5.73
25	g	CH3	p-	A	2.98	5.53	5.53
26	a	H	m-	B	2.14	5.67	5.68
27	a	H	p-	B	0.42	6.38	6.56
28	b	H	m-	B	0.49	6.31	5.92
29	b	H	p-	B	0.27	6.58	6.80
30	**c**	**H**	**m-**	**B**	**0.44**	**6.35**	**6.20**
31	c	H	p-	B	0.04	7.46	7.08
32	d	H	m-	B	0.24	6.63	6.29
33	d	H	p-	B	0.05	7.35	7.16
34	**e**	**H**	**m-**	**B**	**0.16**	**6.79**	**6.16**
35	e	H	p-	B	0.10	6.99	7.03

(Table 1) contd….

Cpd*	R_1	R_2	P.	Scaff.	IC_{50exp}(μM)	pIC_{50}exp	pIC_{50}calc
36	a	H	m-	C	3.74	5.43	5.42
37	a	H	p-	C	1.38	5.86	6.30
38	b	H	m-	C	0.69	6.16	5.66
39	**b**	**H**	**p-**	**C**	**0.38**	**6.42**	**6.54**
40	c	H	m-	C	1.48	5.83	5.96
41	c	H	p-	C	0.29	6.54	6.83
42	d	H	m-	C	2.58	5.59	6.07
43	d	H	p-	C	0.15	6.81	6.94
44	d	H	m-	C	0.66	6.18	5.96
45	**d**	**H**	**p-**	**C**	**0.12**	**6.91**	**6.82**

*The compounds marked in bold belong to the test group.

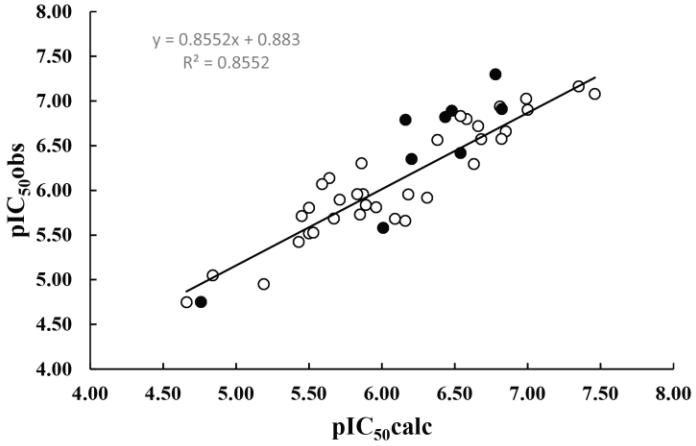


Fig. (19). Graphic representation of pIC_{50}exp versus pIC_{50}calc from selected topological model.

that evaluate fundamentally the topological assembly of molecules) [32], topological charge indices, Gi, Ji, (which evaluate the intramolecular charge transfer) [33] and a group of constitutional indices (including the number of atoms, degree of branching, *etc.*) [34]. Altogether 62 descriptors obtained with the program DESmol1 [35] were calculated.

Multi-linear regression analysis was carried out using the TIs as independent variables and the inhibitory activity, in its logarithmic transformation, pIC50 = -LogIC50, as dependent variable. 80% of the compounds were included in the training group whereas the remaining 20% (molecules marked in bold in Table **1**), were left apart as an external test group for model validation. The selection of both groups was done randomly.

The best regression equation achieved was:

$$pIC_{50} = 4.04 - 5.76(D1) + 13.20(C4P) - 0.81(PR2) \quad \text{Eq. 8}$$

N= 35 r^2=0.855 r^2_{pred} = 0.835 q^2_{cv} = 0.817
SEE = 0.27 F(3,31)=61.0 p>0.00000

The TIs that appear in Eq. 8 evaluate exclusively topological aspects (D1=$^1\chi$-$^1\chi^v$ and C4P=$^4\chi_p$/$^4\chi_p{}^v$) and compounds' degree of branching (PR2).

The equation shows a good statistical record, for example the value of regression coefficient, r^2 = 0.855, is indicative of a high predictive capability. When applying the equation to the external test group, the predictive efficiency remains at the same level, r^2_{pred} = 0.835. The internal validation test (leave-one-out) shows a predictive rate above 80%, Q^2_{cv} = 0.817,

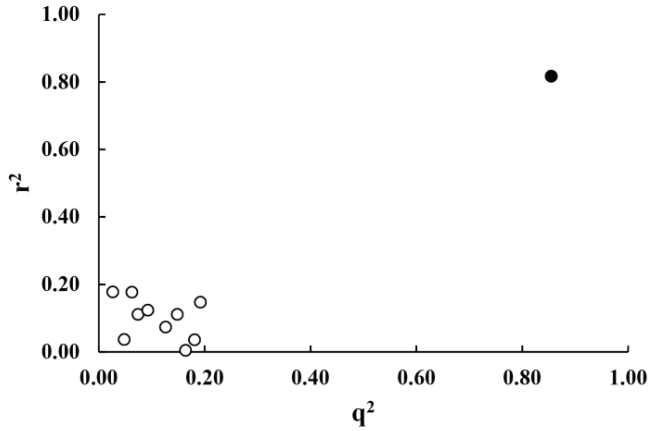


Fig. (20). Graphic representation of q^2_{cv} (prediction coefficient), versus r^2 (correlation coefficient) calculated with randomization test obtained with the selected topological model.

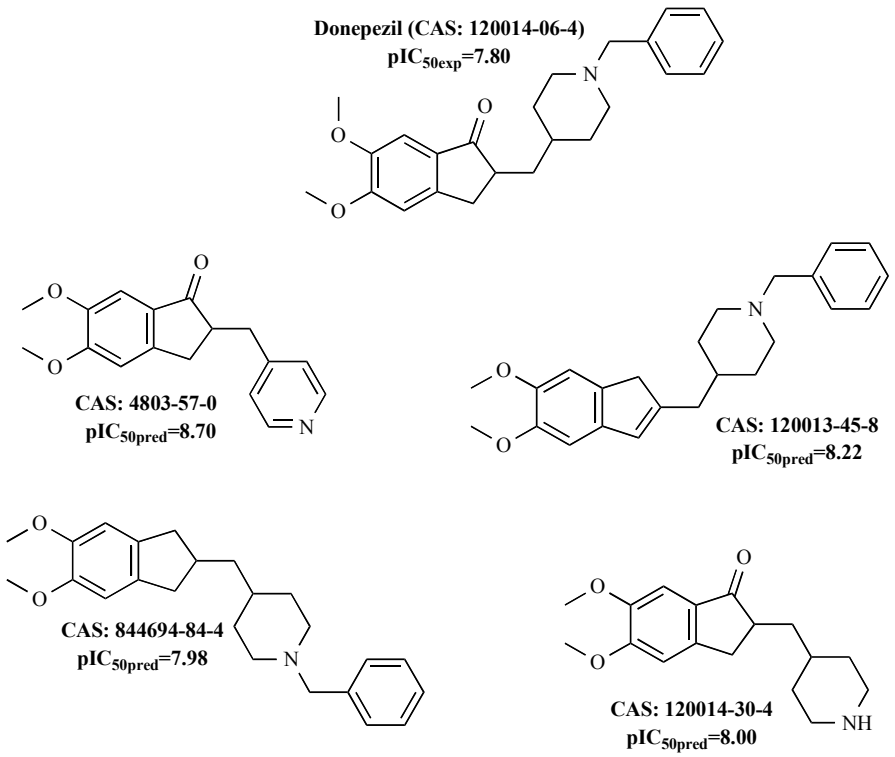


Fig. (21). Selection of potential active agents against AChE, obtained when applying the topological model, Eq. 8, to the virtual screening performed in the ChemIDplus database.

which excludes the presence of outliers among the molecules used in the analysis. In addition, the value of SEE = 0.27 indicates that the uncertainty that accompanies the prediction of activity is 9.6% of the range in which the activity lies. Table **1** and Fig. **19** show the observed and calculated pIC_{50} values.

Furthermore, the test of randomness applied to the training group indicates that the predictive equation is highly stable, although the numerical range of activity is small (pIC_{50min} = 4.66; pIC_{50max} = 7.46) (see Fig. **20**).

Once the mathematical model for AChE inhibitory activity has been validated, it can be used to search new potentially active molecules, within a structural environment similar to that of the reference drug donepezil. As an example, we performed a molecular virtual screening with the help of the ChemIDplus Database [36]. Based on the structure of donepezil, we have indicated that it shows all those molecules registered in the database and that present a structural similarity superior to 70%.

Fig. (**21**) shows some of the molecules selected by the model, all predicted to be more potent than donepezil. The compound CAS: 4803-57-0, with a pCI_{50}pred = 8.70, which implies an IC_{50} of 2nM, stands out as 8-fold more potent than donezepil (IC_{50} = 15.8 nM). The other molecules have a predicted IC_{50} below 10nM.

This example illustrates the potential of MT-QSAR as a robust tool for the search of novel anti-AD candidates, what is nothing else that confirming what already demonstrated experimentally.

CONCLUSION

From what outlined in this review, it is noteworthy that the QSAR methods represent a powerful tool for the search and design of new drugs effective in Alzheimer's disease (AD). However, as was to be expected, the additional use of other complementary techniques, such as those based on molecular mechanics and molecular dynamics or *docking*, allows improved results because they add conformational constraints and, in general 3D features, which are necessary for a correct evaluation of the drug-receptor interaction.

Within the QSAR techniques, those based on molecular topology (MT-QSAR) have shown to be especially effective in the search for new anti-AD drugs. This efficiency has increased over the past 10 years by adding more powerful statistical approaches, such as neural networks, to the traditional ones (multi-linear regression, discriminant analysis, cluster analysis, principal component analysis, *etc*.). This has allowed the use of MT-QSAR to generate patents of several new lead compounds active *in vivo* in animal experiments, including some that follow dual mechanisms of action and that, in principle, are expected to show greater therapeutic efficacy.

Altogether, a renewed interest on the topic may be expected in the next coming years.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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